37. *IN VIVO* FUNCTIONAL GENOMIC SCREEN TO IDENTIFY NOVEL DRIVERS OF LUNG-TO-BRAIN METASTASIS

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Brain metastasis, the most common tumour of the central nervous system, occurs in 20–36% of primary cancers. In particular, 40% of patients with non-small cell lung cancer (NSCLC) develop brain metastases, with a dismal survival of approximately 4–11 weeks without treatment, and 16 months with treatment. This highlights a large unmet need to develop novel targeted therapies for the treatment of lung-to-brain metastases (LBM). Genomic interrogation of LBM using CRISPR technology can inform preventative therapies targeting genetic vulnerabilities in both primary and metastatic tumours. Loss-of-function studies present limitations in metastasis research, as knocking out genes essential for survival in the primary tumour cells can thwart the metastatic cascade prematurely. However, gene overexpression using CRISPR activation (CRISPRa) has the potential for overcoming dependencies of gene essentiality. We theorize that an *in vivo* genome-wide CRISPRa screen will identify novel genes that, when overexpressed, drive LBM. We have developed a patient-derived orthotopic murine xenograft model of LBM using primary patient-derived NSCLC cell lines (termed LTX cells) from the Swanton Lab TRACERx study. We are now poised to transduce LTX cells with a human genome-wide CRISPRa single guide RNA (sgRNA) library, and to subsequently inject the cells into the lungs of immunocompromised mice. We will then track the process of LBM using bioluminescent and MRI imaging until mice reach endpoint. Sequencing of primary lung tumours and subsequent brain metastases promises to uncover enriched sgRNAs, which may represent novel drivers of primary lung tumour formation and LBM. To the best of our knowledge, this study is the first *in vivo* genome-wide CRISPRa screen focused on identifying novel drivers of LBM, and can inform future preventative therapies to improve survival outcomes for NSCLC patients.

38. INNOVATIVE USE OF A CUSTOM MOBILE APPLICATION (APP) BY A BRAIN METASTASES PROGRAM FACILITATES MULTIDISCIPLINARY MANAGEMENT OF PATIENTS AND DECREASED LENGTH OF HOSPITAL STAY (LOS)

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INTRODUCTION: Patients with Brain Metastases (BM) are complex, mandating multidisciplinary care. Our BM patients are discussed at in-person, weekly Brain Tumor Boards (BTB). However, BM patients diagnosed outside weekly BTBs wait several days for the next BTB, causing delays in generating multidisciplinary plans-of-care, prolonging LOS. We created a custom mobile app for our Brain Metastases Program to have a 'Brain Metastases Virtual Tumor Board' (BMVTB) discussion, in real-time, resulting in faster plans-of-care, decreasing LOS. METHODS: The current pathway for navigating multidisciplinary discussions for patients with BM was examined by members of our Brain Metastases Program. We identified the need for all disciplines to participate in a BMVTB, outside of our in-person, weekly BTB. We developed a secure app that can be downloaded on any provider's mobile device. The app includes a digital BM treatment algorithm for providers to understand comprehensive, data-driven, BM management. The app also gives our multidisciplinary Brain Metastases Program access to a BMVTB messenging tool to securely communicate and generate real-time consensus plans-of-care. Using a Vizient Clinical Database, we retrospectively calculated LOS index (observed LOS/expected LOS) for 184 BM patients over 21 months, creating a baseline. After launching our app and BMVTB workflow we prospectively evaluated LOS index in 45 BM patients over 6 months. RESULTS: Over 21-months, 184 patients demonstrated baseline LOS index of 1.073. After launching our mobile app and BMVTB workflow, 45 patient admissions over 6-months demonstrated LOS index of 0.850. Using Levene's test for equal variances, LOS variance with the app and BMVTB was lower than LOS variance at baseline ($p = 0.049$). This demonstrates a 38% reduction in LOS when the app and BMVTB generated real-time plans-of-care. CONCLUSION: We demonstrated utility of a custom BM app coupled with a BMVTB to generate real-time plans-of-care for BM patients, reducing LOS.

39. CHARACTERIZING NOVEL INHIBITORS OF BRAIN METASTASIS-INITIATING CELLS

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BACKGROUND: The incidence of brain metastases (BM) is tenfold higher than primary brain tumors. BM commonly originate from primary lung, breast, and melanoma tumors with a 90% mortality rate within one year of diagnosis. Current standard of care for BM includes surgical resection with concurrent chemoradiation, but does not extend median survival past 16 months, posing a large unmet need to identify novel therapies against BM. METHODS: From a large in-house biobank of patient-derived BM cell lines, the Singh Lab has generated murine orthotopic patient-derived xenograft (PDX) models of lung, breast, and melanoma BM that recapitulate the stages of BM progression as seen in human patients. Using these three PDX models, we identified a population of "pre-metastatic" brain metastasis-initiating cells (BMICs) that are newly arrived in the brain but have yet to form detectable tumors. Pre-metastatic BMICs are not detectable in human patients but are important therapeutic targets with the potential to prevent BM in at-risk patients. RESULTS: RNA sequencing of pre-metastatic BMICs from all three PDX primary tumor models with subsequent Connectivity Map analysis identified novel compounds that have the potential of killing all three types of BMICs. In particular, we identified two compounds that have selective killing of BMICs *in vitro* from all three primary tumor cohorts while sparing non-cancerous cells. We further characterized their ability to inhibit the self-renewal and proliferative properties of BMICs. Ongoing *in vivo* work will investigate the compounds' preclinical utilities in preventing BM. CONCLUSION: Identification of novel small molecules that target BMICs could prevent the formation of BM completely and dramatically improve the prognosis of at-risk cancer patients.

40. AN UPDATE ON THE DEVELOPMENT OF A NEW TOOL TO ASSESS RESPONSE IN LEPTOMENINGEAL METASTASIS

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In 2016, a standardized scorecard to aid in the evaluation of MRI findings during the course of disease was proposed by the RANO leptomeningeal metastasis (LM) subcommittee. In this scorecard, LM main features and the different CNS metastases types were to be reported as present or absent, dimensions of measurable nodules were to be noted, and changes from the previous MRI were to be scored from -3 to +3. A feasibility and validation study of this scorecard was performed by asking 19 experts to evaluate response in 22 patients diagnosed with and treated for LM. The outcome was disappointing in that the scorecard appeared to be too complicated (Le Rhun et al. Neuro-Oncology 2019;21:648–658). Specific challenges were (i) to understand that the form should be used to rate the current MRI and to compare it with the previous one, (ii) to use the proposed rating with "minus" or "plus" options to assess the change and (iii) to derive a sum score that does not take into consideration (per instruction) changes for the items "hydrocephalus", "brain metastases" and "parenchymal medullary metastases". In addition to the apparent challenges for experienced raters to use the LANO scorecard instructions without further instructions, we identified additional weaknesses. These include to eliminate epidural metastases from response assessment, to include the definition of a nodule, the distinction of leptomeningeal versus parenchymal brain disease, and to include parallel, but clearly separate criteria to document brain parenchymal disease. The revised, published proposal for a new scorecard has been used to rate another series of LM cases by experienced neuro-oncologists from March to May 2020. First analyses of this novel feasibility and validation study will be available in August.

41. PROGNOSTIC VALIDATION OF THE EANO ESMO CLASSIFICATION OF LEPTOMENINGEAL METASTASIS

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BACKGROUND: The EANO ESMO guidelines have proposed a classification of leptomeningeal metastases (LM) based on clinical (typical/atypical), cytological (positive/negative/equivocal) and MRI (A linear, B nodular,